

Update on the diagnosis and management of Behçet's disease

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Abstract: Behçet's disease is a multi-organ disorder that is more common in countries around the Silk Road, and manifests as mucosal ulcers and skin lesions, and with ocular involvement. As a systemic disease, it can also involve gastrointestinal organs and the central nervous or cardiovascular systems. Although the etiology of Behçet's disease is not clearly identified, the pathogenesis of the disease is most commonly hypothesized as a profound inflammatory response triggered by an infectious agent in a genetically susceptible host. As there are no single specific manifestations or specific diagnostic tests, various diagnostic criteria have been proposed around the world, and, among them, the International Study Group criteria have been most commonly used. As the clinical expression of Behçet's disease is heterogeneous, the treatment should be individualized based on involved organs, severity of the disease, and patient's background. The choice of therapeutic agents is limited by lack of clinical trials and is based largely on case reports, case series, and several open-label clinical trials. Corticosteroids, colchicine, and traditional immunosuppressive agents, including azathioprine and cyclosporine, have been used for the treatment of Behçet's disease. Recently, tumor necrosis factor (TNF) inhibitors have become available for several rheumatic diseases, and considerable published data suggest that TNF inhibitors represent an important therapeutic advance for patients with severe and resistant disease, as well as for those with contraindications or intolerance to these treatments.

Keywords: Behçet's disease, therapeutic agents, etiology, diagnosis

Introduction

Behçet's disease is a multi-organ disorder characterized by recurrent mucosal ulcers, ocular inflammation, skin lesions, gastrointestinal disease, and musculoskeletal involvement. It was first described by Hippocrates but was brought to attention in 1937 by Hulusi Behçet, a Turkish dermatologist from Istanbul, who reported three patients with recurrent oral and genital ulceration, hypopyon uveitis, and erythema nodosum.¹ The etiology of Behçet's disease remains unknown, but the most widely held hypothesis of disease pathogenesis is that a profound inflammatory response is triggered by an infectious agent in a genetically susceptible host.²

Epidemiology

Behçet's disease is commonly seen along the ancient Silk Road, which extends from Eastern Asia to the Mediterranean region; its prevalence is highest in Turkey, where it was first reported. The comparative prevalence in different countries is shown in several studies.³⁻¹³ The usual age of onset is between the second and fourth decades. Younger patients (age of onset ≤ 24 years) have a higher prevalence of eye disease and total clinical activity than older patients (age of onset ≥ 25 years).¹⁴ The disease is more common in

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females in Asian countries, while the opposite is true in the Mediterranean population.¹⁵

The etiology of Behçet's disease is unknown, but both genetic background and environmental factors are thought to be associated with the development and progression of the disease. For instance, the presence of human leukocyte antigen (HLA) B51 increases the risk of developing Behçet's disease in different ethnic groups 1.5- to 16-fold,^{16–18} and patients who have this allele have a higher incidence of posterior uveitis than those without it. On the other hand, some reports suggest a role of environmental factors in susceptibility to the disease. Infectious agents, such as *Streptococcus sanguis*,¹⁹ Herpes simplex virus,²⁰ hepatitis viruses, and parvovirus B19 have been implicated as causes of Behçet's disease.²¹ Interestingly, Turkish immigrants to Germany have a significantly lower risk of developing Behçet's disease than those of Turkish origin still living in Turkey. Similarly, the disease is quite rare among Japanese immigrants in Hawaii and California, despite a high prevalence in Japan.²²

Diagnosis

Since there is no single test for diagnosing Behçet's disease, several criteria sets existed for Behçet's disease up to 1990. In 1990, the International Study Group (ISG) for Behçet's disease proposed the first evidence-based criteria.²³ According to the criteria, patients must have oral (aphthous) ulcers as well as two of the four other findings. It should be noted that this criteria was for research classification purposes. Clinicians should not rely on these criteria, since Behçet's disease can start with serious manifestations such as pulmonary aneurysms or uveitis without meeting the classification criteria. The differential diagnosis comprises herpes simplex infection, HLA B-27-associated diseases, human immunodeficiency virus infection, inflammatory bowel disease, and other rheumatic diseases. In Japan, the criteria of the Behçet's Disease Research Committee of Japan is most frequently used,²⁴ and a recent large study has demonstrated high concordance rates for ISG and Japanese criteria fulfillment in US and Japanese patients with Behçet's disease.²⁵ In the Japanese criteria, arthritis, epididymitis, gastrointestinal lesions, vascular lesions, and genital ulcers are defined as additional symptoms, and patients with gastrointestinal, vascular, or neuronal lesions are classified as special types. The International Criteria for Behçet's Disease (ICBD) is one of the latest proposed criteria sets, created with the participation of 27 countries from different parts of the world. In one study that compared the diagnostic performance of ICBD criteria with the ISG criteria in three independent cohorts, the ICBD

criteria shows a higher sensitivity and accuracy than the ISG criteria in all three population groups.²⁶

Clinical manifestations

Oral ulceration

One of the most characteristic signs of Behçet's disease is recurrent stomatitis, which can be seen in 97%–100% of the patients.²⁷ It is usually the initial symptom, and often precedes diagnosis by several years.²⁸ Oral ulcers are similar to common mouth ulcers in appearance and localization. The typical lesion is round, well defined, and covered with a yellowish pseudomembrane. Lesions may occur singly or in crops, and subside within a few weeks. The most common sites of oral ulceration are the tongue, lips, and gingival and buccal mucosa, although involvement of the palate, pharynx, and tonsil can also occur. Oral ulcerations can be classified as minor, major, or herpetiform based on their characteristics. Minor ulcers are defined as isolated or multiple, shallow, and small (<10 mm), and usually heal without scarring. Major ulcers are larger (>10 mm), deeper, and more painful than minor ulcers. Herpetiform ulcers refer to numerous shallow, small, pinpoint (1–2 mm in diameter) lesions, occurring as clusters. Herpetiform ulcers sometimes enlarge and coalesce to form large ragged ulcers, which can heal with scarring.²⁹ Incidental trauma such as tooth brushing, gum chewing, or eating foods with sharp and rough textures can trigger the formation of aphthous ulcers.³⁰ Oral ulceration that recurs more than three times in 1 year is required to meet the diagnostic criteria for Behçet's disease.

Urogenital lesions

Genital ulcers occur in more than 70% of cases, and are morphologically similar to oral ulcers, but they are frequently larger, deeper, and heal with scarring.²⁸ In males, they most commonly occur on the scrotum; penile lesions are uncommon. Epididymitis is also common, but urethritis is not a feature of Behçet's disease, which may be useful in distinguishing it from Reiter's syndrome. In female patients, ulcers occur on the vulva, vagina, and cervix and may cause dyspareunia. Groin, perianal, and perineal ulcers occur in both sexes.²⁹

Ocular disease

Eye involvement occurs in 30%–70% of patients with Behçet's disease, and it is more common and more severe in men than in women. The typical form of ocular involvement is a relapsing–remitting uveitis. Chronic and recurrent anterior uveitis can result in hypopyon, which is characterized by

accumulation of white blood cells in the anterior chambers of the eye. Less commonly, conjunctivitis, conjunctival ulcers, keratitis, episcleritis, scleritis, and extra-ocular muscle paralysis may occur as a result of the neurological activity of Behçet's disease. Intraocular inflammation may involve the anterior or posterior segment, or, more commonly, both segments. The classification of uveitis as anterior or posterior type is important both therapeutically and prognostically because those lesions affecting the posterior segment are of a persistent nature, and correlate with significant visual loss.³¹ Other ocular lesions include vitreous hemorrhage, optic neuritis, retinal vein occlusion, and retinal neovascularization.³²

Skin disease

Skin disease occurs in over 75% of patients with Behçet's disease.³³ Erythema nodosum usually occurs in the lower extremities and is characterized by red, painful nodules 1–5 cm in diameter. They are more commonly observed in female patients, and they heal with pigmentation in 1–6 weeks. Histopathology frequently shows septal panniculitis, although lobular panniculitis and vasculitis are also observed. Acneiform lesions are another common presentation of the disease. Although its appearance is similar to ordinary acne, and it appears on the usual acne sites, such as the face, back, and chest, it also occurs on unusual sites such as the arms and legs. The pustules are not usually sterile, and the microbiology is similar to that of acne vulgaris except that *Staphylococcus aureus* is more common and coagulase negative staphylococci is less common in patients with Behçet's disease.³⁴ Pathergy is skin hyper-reactivity to trauma such as needle puncture, and it manifests as an erythematous papular or pustular reaction to skin injury. Development of papules and pustules 48 hours after insertion of 20-gauge needles in hairless areas of the forearm is considered a positive test for pathergy. The rate of positivity is lower in North American and North European patients than in Middle Eastern patients.³⁵ Interestingly, compared with 35 years ago, the sensitivity of the pathergy test has dropped to 35.8%, while the specificity has improved from 86.6% to 98.4%.³⁶

Musculoskeletal disease

Non-erosive arthritis is seen in about 50% of patients with Behçet's disease. The arthritis is usually monoarthritis or oligoarthritis, affecting the medium and large joints such as knee, wrist, and ankle. The arthritis typically resolves within a few weeks. In contrast to HLA B-27-associated diseases,

sacroiliitis is rare in patients with Behçet's disease.³⁷ Patients with Behçet's disease who have arthritis tend to have more acne and enthesopathy,³⁸ suggesting that these symptoms can be considered as one cluster. A recent study showed significant familial clustering of acne/arthritis/enthesitis, which supports a hypothesis that a common genetic pathway is involved in its clinical presentation.^{39,40}

Gastrointestinal disease

The frequency of gastrointestinal involvement varies depending on geographic location and ranges from 3% to 50%. Gastrointestinal involvement causes anorexia, abdominal pain, diarrhea, melena, and perforation. Ulceration is seen usually in the terminal ileum, cecum, and ascending colon, but virtually any part of the gastrointestinal tract can be affected. Clinically, ulceration associated with inflammatory bowel disease is often indistinguishable from that of Behçet's disease. In addition, these diseases share features such as oral ulceration, arthritis, uveitis, and erythema nodosum. Thus, special consideration is required before making the diagnosis of Behçet's disease in patients with gastrointestinal involvement.^{41–45}

Neurologic disease

Central nervous system (CNS) involvement in Behçet's disease, usually called neuro-Behçet's disease, is one of the most serious manifestations, occurring in less than 20% of cases. Male predominance was reported in patients with CNS involvement.⁴⁶ Of patients with CNS disease, 70%–80% have parenchymal involvement, and the brain stem is the most commonly affected site.⁴⁷ Typically, neurologic symptoms such as meningoencephalitis, neurologic deficits, and psychiatric symptoms (including personality changes) develop several years after diagnosis. Non-parenchymal involvement may be observed as intracranial hypertension due to dural sinus thrombosis and presents with headaches and papilledema. The symptoms recur many times and gradually result in irreversible neural injury. Neuroimaging has a significant role in the diagnosis of CNS involvement. Abnormalities detected by magnetic resonance imaging (MRI) have been well described in CNS disease.⁴⁸ Cerebrospinal fluid (CSF) may show increased protein and increased cells, usually neutrophil predominant.

Vascular disease

Vascular involvement occurs in about 25% of patients with Behçet's disease, with a predilection for veins.⁴⁹ Superficial thrombophlebitis and deep venous thrombosis are the most

common venous complications. Occlusion of vena cava superior or inferior, dural sinus, and Budd–Chiari syndrome have also been reported.⁵⁰ The coagulation system is usually intact; therefore, the formation of thrombi may occur due to endothelial cell injury rather than increased thrombin generation.^{51–53} The frequency of arterial lesions is relatively low, ranging from 1% to 33.5% of all vascular involvement,⁵⁴ and the mortality rate in patients with arterial involvement is reported to be higher than in those without it.⁵⁵ Involvement of the aorta and pulmonary artery can cause serious aneurysm formation or occlusion, and pulmonary aneurysm is one of the most significant causes of death due to life-threatening hemorrhage in patients with Behçet's disease.⁵⁶

Management

Treatment options depend on the affected organ and its severity. It is important to prioritize therapeutic options according to the disease type, severity, age, and sex of each patient. Special attention should be paid to ocular, vascular, and neurologic disease, because they are the most serious manifestations and require more aggressive treatment.

Corticosteroids

Topical corticosteroids are beneficial for oral and genital ulcerations, and can be the first-line treatment, especially for patients with mild disease, while systemic corticosteroids are the recommended treatment for patients with moderate to severe disease with ocular, vascular, gastrointestinal, or neurological involvement.⁵⁷ Although corticosteroids are widely used for patients with Behçet's disease, there has been only one placebo-controlled trial, in which 86 patients who had active disease with genital ulcer were randomized for administration of either intramuscular methylprednisolone 40 mg or placebo every 3 weeks for 27 weeks. The result showed no significant differences in the mean number of genital and oral ulcers or folliculitis between the groups. However, the mean number of erythema nodosum lesions was less in the corticosteroid group as a whole; subgroup analyses revealed that this was significant for female patients but not for male patients.⁵⁸ Although corticosteroids are effective in decreasing acute inflammation, systemic corticosteroids alone often fail to prevent recurrences in cases with ocular involvement. They are generally used in combination with other immunosuppressive drugs.⁵⁹ Intravitreal triamcinolone acetonide injection may be used as adjunct therapy for the treatment of refractory panuveitis or in patients who were intolerant to systemic corticosteroids.⁶⁰

Colchicine

Colchicine has been used for the treatment of Behçet's disease, particularly for mucocutaneous disease. The anti-inflammatory effect of colchicine has been attributed to its disruption of microtubules in neutrophils, thereby inhibiting their migration toward chemotactic factors. In one randomized controlled trial, use of colchicine significantly reduced the rate of genital ulcers, erythema nodosum, and arthritis associated with Behçet's disease, especially among female patients.⁶¹ A more recent double-blinded, placebo-controlled crossover trial concluded that colchicine significantly improved the overall Disease Activity Index score.⁶² However, patients may develop significant gastrointestinal intolerance if the medication is taken at doses higher than 1.5 mg/day.

Azathioprine

Azathioprine is a purine synthesis inhibitor and one of the most widely used immunosuppressive medications for Behçet's disease. In the only placebo-controlled trial, 73 patients who had Behçet's disease with or without ocular involvement, were randomly assigned for treatment with either azathioprine (2.5 mg/kg/day), or placebo. After 2 years of follow-up, the patients taking azathioprine developed less ocular disease and experienced less frequent ocular complications, oral ulcers, genital ulcers, and arthritis.⁶³ A long-term follow-up further confirmed the beneficial effects of azathioprine in these patients.⁶⁴ Recently, a retrospective analysis of 157 consecutive patients with severe uveitis (active posterior uveitis or panuveitis) treated with corticosteroids (0.5–1 mg/kg/day) and azathioprine (2.5 mg/kg/day) revealed that posterior uveitis was controlled in 92.9% of patients, of whom 51.6% were complete responders and 41.4% were partial responders.⁶⁵

Cyclosporine

Cyclosporine, a calcineurin inhibitor that affects both T-cell and B-cell proliferation,⁶⁶ is commonly used for uveitis associated with Behçet's disease. Three controlled trials have evaluated the efficacy of cyclosporine in patients with Behçet's disease. A single-masked trial of cyclosporine 5 mg/kg/day versus a monthly 1 g intravenous bolus of cyclophosphamide was conducted among 23 patients with Behçet's disease who had active potentially reversible uveitis. During the initial 6 months, patients in the cyclosporine group showed a significant improvement in visual acuity. However, the subsequent follow-up of patients up to 24 months suggested that this effect was not sustained.⁶⁷ In a randomized, double-masked trial, 96 patients with

active ocular disease were treated with either cyclosporine (10 mg/kg/day) or colchicine (1 mg/day). After 16 weeks, cyclosporine was more beneficial than colchicine in reducing the frequency of ocular attacks, alleviation of such attacks, and improvement of visual acuity as well as extra-ocular manifestation such as oral aphthous ulcer, dermal lesions, and genital ulceration.⁶⁸

Despite its efficacy in treating many manifestations of Behçet's disease, cyclosporine appears to cause neurotoxicity or accelerates the development of CNS symptoms.⁶⁹ In these cases, there may be some selection bias because there is an association between neurologic and eye involvement – the main indication for the use of cyclosporine in Behçet's disease.⁷⁰ However, in a large retrospective analysis that compared patients treated with cyclosporine, other immunosuppressive drugs, and colchicine, parenchymal neurologic involvement was observed more frequently in the cyclosporine-treated group, even after adjusting for disease severity.⁷¹

Thalidomide

Thalidomide was developed in the 1950s as a sedative drug and was withdrawn in 1961 because of its teratogenic effects. However, it has been rediscovered recently as an immunomodulatory drug that suppresses tumor necrosis factor (TNF)- α -induced nuclear factor (NF)- κ B activation and adenosine triphosphate (ATP)-induced interleukin (IL)-1 β secretion.⁷² By modulating the activity of NF- κ B, thalidomide can up-regulate the expression of downstream genes involved in the pathophysiology of Behçet's disease. Thalidomide has been reported to be effective in treating patients with mucocutaneous lesions.^{73,74}

Cyclophosphamide

Although a systematic review of the Cochrane database concluded that there was not enough evidence to support the use of cyclophosphamide in the treatment of Behçet's disease, particularly the ocular manifestations,⁷⁵ it still can be a choice for life-threatening manifestations. According to The European League Against Rheumatism (EULAR) recommendations, use of cyclophosphamide is advocated for major vessel disease, pulmonary artery disease, and CNS disease.

Interferon- α

Although the mechanism of action of interferon (IFN)- α in Behçet's disease remains elusive, it has been administered for various manifestations of Behçet's disease, first by

Tsambaos et al,⁷⁶ because of its antiviral and anti-proliferative properties. One large literature review, which included data on IFN α treatment published between 1986 and 2002, revealed that IFN α treatment was effective in 86% of patients with mucocutaneous disease, 96% with arthritis, and 94% with ocular uveitis.⁷⁶ Higher IFN α doses were more effective than low-dose regimens, and led to up to 56% long-term remissions even after discontinuation of the IFN α . Side effects were dose-dependent and similar to those noted in patients with hepatitis C.⁷⁷

Tumor necrosis factor- α inhibitors

Evidence is emerging that anti-TNF α agents are highly effective for patients with Behçet's disease. Among them, infliximab has been most frequently used, mainly for refractory ocular Behçet's disease. Although there have been no controlled trials, a considerable number of observational studies have reported that infliximab reduces the frequency of uveitis attacks, successfully treats refractory macular edema, and improves visual acuity.^{78–83} Only one prospective study from Japan has evaluated the efficacy of infliximab, using 3–5 mg/kg body weight every 8 weeks in patients with gastrointestinal disease. In this study, all patients showed improvement of gastrointestinal symptoms and disease-associated complications within 4 weeks. Furthermore, the rate of disappearance of ileocecal ulcerations was 90% after 1 year.⁸⁴ Although there have been no prospective studies, some case reports or case series suggest the efficacy of infliximab for treating vascular and neurologic disease.^{85–87}

Etanercept is the only TNF inhibitor evaluated in a randomized trial. In the trial, 40 patients with mucocutaneous disease and/or arthritis were assigned to either etanercept (25 mg subcutaneously twice a week) or placebo injections for 4 weeks. The mean numbers of oral ulcers, nodular lesions, and papulopustular lesions were lower in the etanercept group than in the placebo group at almost all weekly evaluations.⁸⁸

Conclusion

The management of Behçet's disease has markedly improved, with better use of conventional medications and the development of newer agents such as biologics. This is especially beneficial for patients with severe or life-threatening disease. Indeed, the morbidity and mortality of Behçet's disease have dramatically changed during the last 2 decades.^{89–91} However, large, well designed trials and more advanced translational research are still needed to develop better diagnostic and management strategies for this complex disease.

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